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**From:** Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]  
**Sent:** 10/9/2019 5:15:54 PM  
**To:** Jerry Campbell [JCampbell@ramboll.com]; Harvey Clewell [HClewell@ramboll.com]  
**CC:** Walsh, Patrick [patrick-walsh@denka-pe.com]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Cascio, Wayne [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a1bd931ca2f84ea8ac2f4c44538f3589-Cascio, Wayne]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Lavoie, Emma [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ac7844f12646c095e4e9093a941623-Lavoie, Emma]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Kirby, Kevin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cbb65672f6f34545be460a66ff6fa969-Kirby, Kevin]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Morozov, Viktor [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=03cc9abb639c453fab2bbb3e4617228-Morozov, Viktor]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; White, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4e179825823c44ebbb07a9704e1e5d16-White, Paul]; Hawkins, Belinda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=075561d171e845828ec67a945663a8e6-Hawkins, Belinda]  
**Subject:** RE: Chloroprene PBPK: Peer review charge questions

Jerry, all,

That may be for the best. We are trying to move ahead in parallel with the contract for the external review. The set of charge questions should not depend on modest changes such as this, so hopefully you can still get back to us in the meantime if there are any significant issues you see there. But does this mean we really need to finish the QA, in case there any other updates needed for the report, before we go ahead with that?

Part of the work is identifying external reviewers and all that, so maybe the contract can proceed to start that process based on the current draft.

-Paul

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**From:** Jerry Campbell <JCampbell@ramboll.com>  
**Sent:** Wednesday, October 09, 2019 11:54 AM  
**To:** Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>  
**Cc:** Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>  
**Subject:** RE: Chloroprene PBPK: Peer review charge questions

Paul,

You are absolutely correct. The figure you derived from the model is the correct figure for the female mouse in vivo study. I had hoped to determine the source of the incorrect figure but I do not have a version of the model going back to

Yuching's original model that generates the figure included in the report so I am at a loss to explain the origin. It is my fault it wasn't updated in the final report. I have corrected the report figure but it sounds like we should hold off on sending you the revision in case any other questions need to be addressed as you complete your QA.

Regards,

**Jerry Campbell**

Managing Consultant

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**From:** Schlosser, Paul <[Schlosser.Paul@epa.gov](mailto:Schlosser.Paul@epa.gov)>

**Sent:** Monday, October 7, 2019 1:34 PM

**To:** Harvey Clewell <[HClewell@ramboll.com](mailto:HClewell@ramboll.com)>; Jerry Campbell <[JCampbell@ramboll.com](mailto:JCampbell@ramboll.com)>

**Cc:** Walsh, Patrick <[patrick-walsh@denka-pe.com](mailto:patrick-walsh@denka-pe.com)>; Thayer, Kris <[thayer.kris@epa.gov](mailto:thayer.kris@epa.gov)>; Cascio, Wayne <[Cascio.Wayne@epa.gov](mailto:Cascio.Wayne@epa.gov)>; Jones, Samantha <[Jones.Samantha@epa.gov](mailto:Jones.Samantha@epa.gov)>; Lavoie, Emma <[Lavoie.Emma@epa.gov](mailto:Lavoie.Emma@epa.gov)>; Bahadori, Tina <[Bahadori.Tina@epa.gov](mailto:Bahadori.Tina@epa.gov)>; Kirby, Kevin <[KIRBY.KEVIN@EPA.GOV](mailto:KIRBY.KEVIN@EPA.GOV)>; Vandenberg, John <[Vandenberg.John@epa.gov](mailto:Vandenberg.John@epa.gov)>; Morozov, Viktor <[Morozov.Viktor@epa.gov](mailto:Morozov.Viktor@epa.gov)>; Davis, Allen <[Davis.Allen@epa.gov](mailto:Davis.Allen@epa.gov)>; White, Paul <[White.Paul@epa.gov](mailto:White.Paul@epa.gov)>; Hawkins, Belinda <[Hawkins.Belinda@epa.gov](mailto:Hawkins.Belinda@epa.gov)>

**Subject:** RE: Chloroprene PBPK: Peer review charge questions

Harvey, Jerry, all,

I assume the draft charge questions have been sent to you by now. I realized there's a mistake in the 2<sup>nd</sup> question in the section titled, "Estimation of Metabolic Parameters from In Vitro Metabolism Experiments." I had thought that the data (and model parameters) used were from male mice (data in original Himmelstein papers, 2004), but I now realize these are female mouse data! I've also run into an issue with reproducing those model results.

A bit more of an introduction to the question may be helpful, pointing out that these are female data and predictions, but I thought also that the review could be helped by showing predictions for both male and female mouse parameters, to demonstrate the impact of the sex difference.

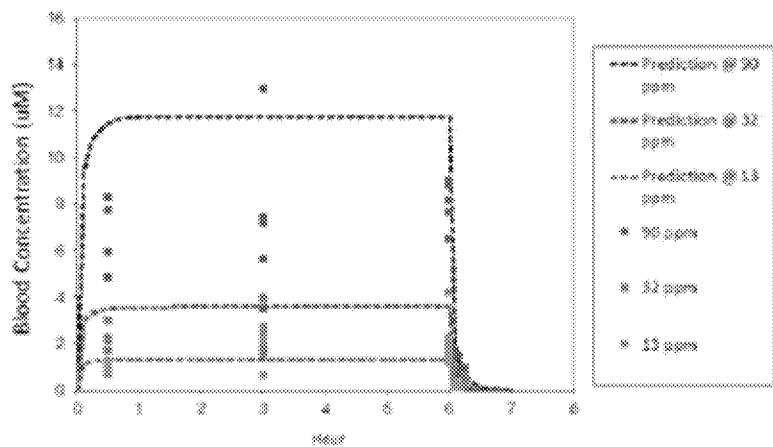
Setting up to create such a plot, I have hit upon a QA issue: the results I get using the script Fmouse\_InVivo.R do not match those shown in Figure 4 of the report. First below is Figure 4 (left panel), 2<sup>nd</sup> is the plot I first got from just running Fmouse\_InVivo.R (files dated 7/16/2019), and third includes dashed lines with predictions using male mouse metabolic parameters. The simulations I'm getting with the package are a lot higher than those shown in the report, which look more like Excel plots in format.

Our intention was to do the QA as the peer review contract was being set up. I'll have to complete my review as soon as possible, so we can resolve any such discrepancies before the material is sent to the reviewers.

-Paul

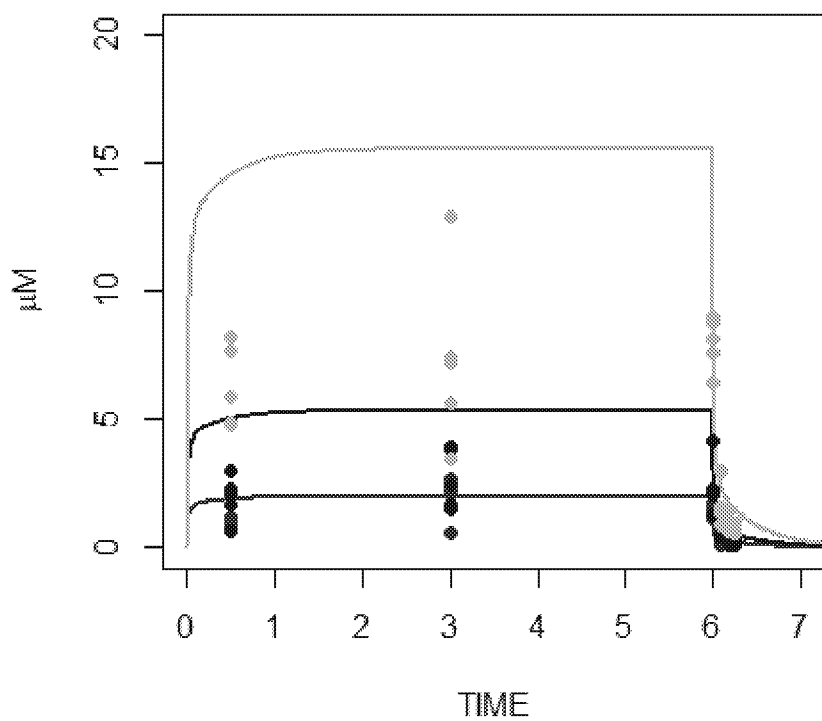
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Figure 4 (left panel) from report:



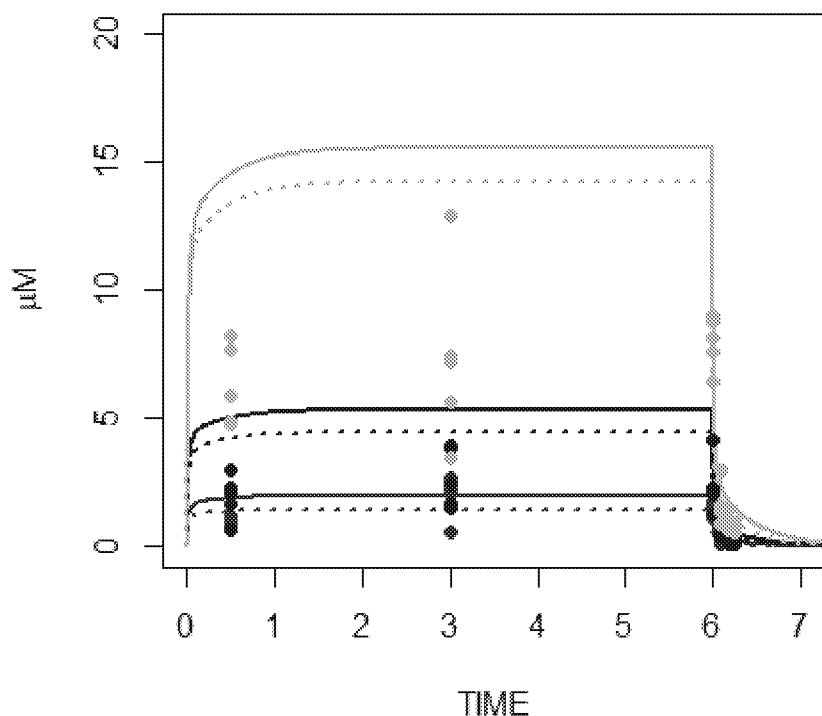
Fmouse\_InVivo.R:

### Mouse Study 3 Week - Day 1



Fmouse\_InVivo.R with simulations using male mouse parameters (dashed lines) added:

## Mouse Study 3 Week - Day 1



**From:** Vandenberg, John <[Vandenberg.John@epa.gov](mailto:Vandenberg.John@epa.gov)>

**Sent:** Wednesday, October 02, 2019 4:46 PM

**To:** Walsh, Patrick <[patrick-walsh@denka-pe.com](mailto:patrick-walsh@denka-pe.com)>

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**Subject:** Chloroprene PBPK: Peer review charge questions

**Importance:** High

Patrick,

We've been diligently evaluating the Ramboll report and conducting analyses related to physiologically-based pharmacokinetic parameters and modeling of chloroprene (references below).

We are moving forward to arrange through a contractor an independent letter peer review by appropriate experts.

In addition to the Ramboll report, we are providing an EPA analysis that we wish to have peer reviewed.

Per our discussion early this summer, we are providing for your information the attached draft Charge questions that will be addressed by the peer reviewers, plus an EPA analysis that we have developed.

Please let us know within a week (by next Wednesday) if you have any major comments on the Charge questions. We are not seeking any comments on the EPA analysis.

Thank you,

John

John Vandenberg, PhD  
Director, Health and Environmental Effects Assessment Division  
Center for Public Health and Environmental Assessment/ORD  
U.S. Environmental Protection Agency/B243-01  
Research Triangle Park, NC 27711  
(919) 541-4527

#### References:

- Ramboll. (2019). Incorporation of in vitro metabolism data in a physiologically based pharmacokinetic (PBPK) model for chloroprene.
- U.S. EPA. (2019). In Vitro to In Vivo Extrapolation (IVIVE) of Metabolism and Non-Enzymatic Conjugation of (1-chloroethenyl)oxirane (1-CEO) and Estimation of Total 1-CEO Clearance in the Liver and Lung of Mice, Rats, and Humans.